PATENT COOPERATION TREATY

To: HOIBERG AS			PCT				
ore Kongensgade 59 A 64 Copenhagen K ANEMARK	AFCEIVED • § § NOV. 2005 HOIBERG	WRITTEN OPINION (PCT Rule 66)					
·		Date of malling (day/month/year)	24.11.2005				
Applicant's or agent's file reference P792PC00		REPLY DUE	within / month(s) from the above date of mailing				
International application No. PCT/DK2004/000454	International filing date (day/month/year) 25.06.2004		Priority date (day/month/year) 26.06.2003				
International Patent Classification (IPC) or both national classification and IPC C07K1,04, C07B61,00							
Applicant CARLSBERG AS							

1.	This written opinion is the second drawn up by this International Preliminary Examining Authority.						
2.	This opinion contains indications relating to the following items:						
	ı	\boxtimes	Basis of the opinion				
	11		Priority				
	Ш		Non-establishment of opinion with regard to novelty, inventive step and industrial applicability				
	١٧		Lack of unity of invention				
	٧	X	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement				
	VI		Certain documents cited				
	VII		Certain defects in the international application				
	VIII		Certain observations on the international application				
3.	The applicant is hereby invited to reply to this opinion.						
	When?		See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).				
	How?		By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.				
	Also:		For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.				
	If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.						
4.	The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 26.10.2005						

Name and mailing address of the international preliminary examining authority:

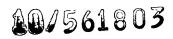


European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswljk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 Authorized Officer

Masturzo, P

Formalities officer (incl. extension of time limits) de Haas, B Telephone No. +31 70 340-4738





IAP20 ROS'6 POTTTO 22 DEC 2005

WRITTEN OPINION

International application No.

PCT/DK2004/000454

 Basis of the opinion 	วท	pinia	10	the	of	is	Bas	I.
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1. With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"):

	Description, Pages							
	1-70)	as originally filed					
	Clai	ims, Pages						
	1-14	13	as originally filed					
	Dra	wings, Sheets						
	1/14	-14/14	as originally filed					
2.	With lang	n regard to the langua guage in which the inte	age, all the elements marked above were available or furnished to ernational application was filed, unless otherwise indicated under	this Authority in the				
	The	se elements were ava	ailable or furnished to this Authority in the following language: ,	which is:				
		the language of publ	inslation furnished for the purposes of the international search (un ication of the international application (under Rule 48.3(b)). Inslation furnished for the purposes of international preliminary example.	. ,,				
3.	With inte	n regard to any nucle rnational preliminary e	otide and/or amino acid sequence disclosed in the international examination was carried out on the basis of the sequence listing:	application, the				
		contained in the inter	rnational application in written form.					
		filed together with the	e international application in computer readable form.					
		furnished subsequently to this Authority in written form.						
	☐ furnished subsequently to this Authority in computer readable form.							
	☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.							
		The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.						
4.	The	amendments have re	esulted in the cancellation of:					
		the description,	pages:					
		the claims,	Nos.:					
		the drawings,	sheets:					
5.		This opinion has been been considered to g	en established as if (some of) the amendments had not been made go beyond the disclosure as filed (Rule 70.2(c)).	e, since they have				

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Claims

1-143

Inventive step (IS)

Claims

1-143

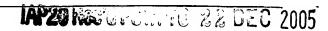
Industrial applicability (IA)

Claims

2. Citations and explanations

see separate sheet

International application No. PCT/DK2004/000454



Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: J. Comb. Chem. 3, 2001, pages 45-63;

D2: J. Comb. Chem. 3, 2001, pages 34-44;

D3: Chemistry - A European Journal 5(4), 1999, pages 1218-1225;

D4: Tetrahedron Lett. 44(19), 5 May 2003, pages 3835-3838.

1) D1 (see i. a. Figure 2) discloses the formation of peptide libraries ending with a polycyclic derivative prepared with the use of the Pictet-Spengler reaction, whose intermediate is known to be an N-acylimminium ion. To this respect see also Scheme 8 of the same document. In particular, scheme 8 of the present document shows an intramolecular Pictet-Spengler reaction which takes places starting from a compound falling into the wording of claims 1ff.

D2 discloses (see Scheme 5) the preparation of peptide isosters ending in a polycyclic derivative by the use of the Pictet-Spengler reaction. These isosters can immediately be used as building blocks in the preparation of libraries, and this is evident already in the title. The use of Pictet-Spengler in this reaction is, however, intermolecular.

D3 discloses the preparation of polycyclic compounds from N-terminal peptide aldehydes immobilized on a support. Though the use of those in the preparation of libraries is not alluded to in the title, it is sufficient to read the first lines of the introduction and the possibility of their use as building blocks in the preparation of libraries becomes evident to the skilled artisan. Figure 1 shows that the Pictet-Spengler reaction leading to cycles can also be intramolecular.

D4 discloses the use of the Pictet-Spengler reaction in the preparation of peptide libraries ending with polycyclic compounds. The examples provided in this disclosure refer only to intermolecular Pictet-Spengler reactions.

On the basis of the above disclosures it is concluded that claims 1-143 of the present application are deemed to lack novelty under Art. 33(2) PCT on the basis of D1 and D3. The applicant is however reminded that the structure of claim 1 ff. is also anticipated in the disclosures D2 and D4, since the definition of "nucleophile" is too generic to permit an

assessment of what is really meant (probably the use of the N-heterocyclic atom of a tryptophane residue as nucleophile).

- 2) On the basis of D1-D4, the objective problem underlying the present application consists in the provision of alternative libraries and method to prepare them. There is no appreciable difference between the present application and the documents cited above. No unsuggested technical feature is evidenced, nor is any surprising effect brought to the attention of the skilled person. Therefore an inventive step under Art. 33(3) PCT cannot be recognized for claims 1-143 of the present application.
- 3) Claims 1-143 are endowed with industrial applicability under Art. 33(4) PCT.